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(54) **Mehod of treatment of rheumatoid arthritis using phytic acid.**

(57) A use is provided in treating rheumatoid arthritis of phytic acid, phytate salt, an isomer or hydrolysate of phytic acid or phytate salt, or a mixture thereof.

Novel pharmaceutical compositions comprise phytic acid, a phytate salt, an isomer or hydrolysate of phytic acid or a phytate salt, or a mixture thereof in combination with a dephosphorylating enzyme, together with a pharmaceutically diluent or carrier.

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**EP 0 420 428 A2**

## METHOD OF TREATMENT OF RHEUMATOID ARTHRITIS USING PHYTIC ACID

The present invention is directed to a use of phytic acid, its salts or hydrolysates, in treating rheumatoid arthritis.

Phytic acid, generally accepted as having the structure myo-inositol-hexakis (dihydrogen phosphate), is a major component of plant seeds, constituting 1-3% by weight of many cereals and oil seeds. Most wheat brans contain between 4 and 5% phytic acid. Phytic acid may be prepared in pure form from various plant sources, such as wheat, corn, soybeans, sesame seeds, peanuts, lima beans, barley, oats, wild rice and sunflower seeds. It can be extracted with dilute hydrochloric acid at room temperature, precipitated with various reagents including ferric chloride, bicarbonates, potassium hydroxide, sodium hydroxide, ammonium hydroxide, calcium hydroxide, magnesium hydroxide or alcohol. It is then further purified by conventional chemical techniques.

When one or more of the acidic protons of the phosphate groups in phytic acid are replaced by a counterion, the compound is usually referred to as a phytate salt. The special name phytin is used for the calcium-magnesium salt of phytate derived from plant seeds (a product of Ciba-Geigy). The present invention includes the use not only of phytic acid and phytate salts, but also various isomeric forms of phytic acid and phytate salts. While the Anderson structure for myo-inositol hexakis dihydrogen phosphate is the generally accepted structure for phytic acid, the present invention covers other isomers which have been previously described in the literature. These isomers include the cis, epi, allo, muco, neo, D-chiro, L-chiro, and scyllo configurations.

Also, while phytic acid contains six phosphate groups, when introduced into the digestive tract of an animal, one or more of the phosphate groups may be hydrolyzed by the action of the digestive acids and enzymes. Therefore, the present invention includes the use of hydrolysates of phytic acid and phytate salts wherein one or more of the phosphate groups have been removed.

The main uses of phytic acid include use as a food additive for preservation of foods. Studies on the use of phytic acid as a food additive show that ingestion of large doses of phytic acid elicits no physiological discomfort or symptoms of any toxicological action in humans. See Starkenstein, *Biochem. Z.* 30: 56 (1911). Phytic acid and its metabolites are thus not believed to be toxic or highly reactive.

Medical applications of phytic acid include use as an imaging agent for organ scintigraphy, an X-ray enhancement contrasting agent and use to

reduce gastric secretion for treatment of gastritis, gastroduodenitis, gastric duodenal ulcers and diarrhea. It has been suggested as an antidote for toxic metal absorption, for therapeutic use in the prevention and dilution of calcium deposits associated with various diseases and for reducing calcium concentration in urine (thus checking the formation of renal calculi). Other uses include as a preventive agent against severe poisoning with pressurized oxygen and preventing thirst during exercise. It has been used as a counterion in salts with various orally administered antibiotics to improve taste.

Phytic acid has also been suggested to reduce the incidence of dental caries, and has been utilized in dentifrices, mouth rinses, dental cements, cleaning agents for dentures and for removing nicotine tar from teeth.

Industrial uses of phytic acid include use as a corrosion inhibitor on metals, a rust remover and an additive to lubricating greases. Other miscellaneous uses of phytic acid include oral administration to treat acne, to improve skin color, blood circulation and fingernail growth; and as an additive in cosmetics for anti-dandruff hair lotions and skin care lotions. One potential agricultural use of phytic acid is to inhibit aflatoxin production by *Aspergillus parasiticus*. It is also useful as an additive to a fermentation medium containing *Micromonospora sagamiensis* in the fermentative production of antibiotics. Similarly, phytic acid may be used as a growth-promoting factor in the fermentation medium for the cultivation of yeast for feed.

For further discussions of industrial applications of phytic acid, see Graf, *JAOCS* 60, 1861-1867 (1983).

Although the above description indicates the broad scope of potential uses of phytic acid, there is not believed to be any suggestion in the prior art that phytic acid is useful for the treatment of rheumatoid arthritis.

Accordingly, we have now discovered that phytic acid, phytate salts, and isomers or hydrolysates thereof, may be used in the treatment of rheumatoid arthritis.

The present invention provides a use of a compound, selected from the group consisting of phytic acid, a phytate salt, an isomer or hydrolysate of phytic acid or a phytate salt, or a mixture of any combination thereof, in treating rheumatoid arthritis. The preferred method of administration is by the oral route.

The use according to the present invention comprises treating a subject, afflicted with rheumatoid arthritis, with a composition in which the active

ingredient is phytic acid, a phytate salt, or an isomer or hydrolysate of phytic acid or phytate salt. By the term isomer as used herein, it is intended to include the various conformations of phytic acid, as described hereinabove, and the corresponding conformations of phytate salts. The term salts is broadly intended to cover any of the various salts formed by the replacement of any or all of the available acidic protons of the phosphate groups with a counterion. The counterion may be any pharmaceutically acceptable counterion such as sodium, magnesium, potassium, zinc, ferric, ferrous, and the like, including organic counterions such as quaternary ammonium ions and ions of organic bases.

The present invention also includes the hydrolysates of phytic acid and phytate salts wherein one or more of the phosphate groups have been removed. Once administered into the digestive tract or bloodstream in the subject, the phytic acid or phytate salt may be hydrolyzed by digestive, blood or cellular enzymes, thereby removing one or more of the phosphate groups on the cyclohexane ring. However, it is contemplated to be within the scope of the invention that these hydrolysates of phytic acid and phytate salts may also be administered directly to the subject and therefore are within the scope of the present invention.

The hydrolysates of phytic acid and phytate salts may be prepared by partial acid or basic hydrolysis or by hydrolysis using enzymes prior to preparation of dosage forms for administration. Preferably, the hydrolysates will be made *in vivo* by coadministering with phytic acid or phytate salt an enzyme which hydrolyzes phosphate groups, such as 3-phytase, 6-phytase or acid phosphatase.

The phytic acid or phytate salt may be absorbed into or adsorbed onto a solid carrier to facilitate pharmaceutical administration. For example, phytic acid may be formulated into a starch powder by spray drying or vacuum drying an aqueous mixture of phytic acid and dextrin.

The preferred compositions for administration, particularly in oral dosage form, are the mono-, di-potassium phytate salts and mixtures thereof which may be prepared from commercially and readily available sodium phytate by initially removing the sodium using ion exchange chromatography on a suitable resin, such as Dowex beads. The free phytic acid may then be treated with potassium hydroxide to convert to the mono- and di-potassium phytate salt.

The preferred method of administration of the compositions according to the present invention is through oral administration in liquid or tablet form. As described hereinabove, the compositions may be administered as pharmaceutically acceptable salts such as salts with alkali metal cations

(sodium, potassium, lithium), ammonium salts and salts with organic bases such as piperidine, triethanolamine, diethylaminoethylamine salts, and the like.

In addition to the active ingredients, the composition may also contain an effective proportion, usually from 0.001 to 0.1% weight by volume, of a pharmaceutically acceptable preservative or sterilizing agent such as cetyl pyridinium chloride, tetradecyltrimethyl ammonium bromide (commercially known as Centramide), benzyl dimethyl [2-(2-p-(1,1,3,3-tetramethyl butyl)) phenoxy] ethoxy ammonium chloride (known commercially as Benzethonium Chloride) and myristyl-gamma-picolinium chloride.

The pharmaceutical composition may also contain conventional excipients, e.g., sodium chloride, dextrose, mannitol, and buffers such as sodium dihydrogen ortho phosphate, disodium hydrogen phosphate, sodium citrate/citric acid, and boric acid/sodium borate. The proportion and concentration of excipients and buffers may be varied within fairly wide ranges, providing the resulting solution is stable and nonirritating when administered. The preferred method of administration is by oral administration as a solid compound. The composition may be prepared in the conventional manner as tablets, pills or powders, using conventional carriers.

The dosage to be administered will vary with the severity of the diseased condition. However, in general, particularly for oral administration, oral administration of from 1/2 to 3 grams of phytic acid (or equivalent phytate salt, isomer or hydrolysate) per kilogram of body weight in the diet per day will usually be effective. Frequency of dosage administration may, of course, be varied as needed and as discretionarily required by the attending physician.

For oral administration, in a preferred embodiment, the active ingredient of the composition will also contain an enzyme such as 3-phytase (EC 3.1.38), 6-phytase (EC 3.1.3.26) or acid phosphatase which, when exposed to the digestive tract, will assist in hydrolyzing one or more of the phosphate groups from the active ingredient. Since phytic acid or phytate salts are not naturally present in animals, the digestive enzymes in animals are believed to be insufficient to completely hydrolyze the phosphate groups. Therefore, to enhance the hydrolysis of the phosphate groups in an animal or man, it is preferred that the active ingredient be administered with one or more of the aforementioned enzymes, with the preferred enzyme being 3-phytase (EC 3.1.38), preferably together with a pharmaceutically acceptable diluent or carrier.

## Claims

1. Use of phytic acid, a phytate salt, an isomer or hydrolysate of phytic acid or a phytate salt, or a mixture thereof for the manufacture of a medicament for treating rheumatoid arthritis.

2. Use as claimed in Claim 1 wherein the phytate salt comprises a potassium salt.

3. Use as claimed in Claim 2 wherein the phytate salt is mono- or di-potassium phytate, or a mixture thereof.

4. Use as claimed in Claim 1 wherein the isomers of phytic acid or phytate salt comprise the hexakisphosphate myo-inositol, scyllo-inositol, D-chiro-inositol, L-chiro-inositol, neo-inositol and muco-inositol conformations.

5. Use as claimed in Claim 4 wherein the isomer of phytic acid or phytate salt is the hexakisphosphate myo-inositol conformation.

6. Use as claimed in Claim 1 wherein the hydrolysate of phytic acid or phytate salt comprises the pentakisphosphate, tetrakisphosphate, triphosphate, diphosphate, monophosphate or completely dephosphorylated hydrolysate.

7. A pharmaceutical composition which comprises phytic acid, a phytate salt, an isomer or hydrolysate of phytic acid or a phytate salt, or a mixture thereof in combination with a dephosphorylating enzyme, together with a pharmaceutically acceptable diluent or carrier.

8. A pharmaceutical composition as claimed in Claim 7 wherein the enzyme is 3-phytase, 6-phytase, acid phosphatase, or a mixture thereof.

9. A pharmaceutical composition as claimed in Claim 7 or Claim 8 wherein the enzyme is 3-phytase EC 3.1.38.

10. A composition which comprises phytic acid, a phytate salt, an isomer or hydrolysate of phytic acid or a phytate salt, or a mixture thereof in combination with a dephosphorylating enzyme, for the use as a medicament for treating rheumatoid arthritis.

11. A composition as claimed in Claim 10 wherein the enzyme is 3-phytase, 6-phytase, acid phosphatase, or a mixture thereof.

12. A composition as claimed in Claim 10 or Claim 11 wherein the enzyme is 3-phytase, EC 3.1.38.

13. A composition as claimed in any one of Claims 10 to 12 which is in the form of a pharmaceutical composition as claimed in Claim 7.

14. Use of phytic acid, a phytate salt, an isomer or hydrolysate of phytic acid or a phytate salt, or a mixture thereof in combination with a dephosphorylating enzyme for the manufacture of a medicament for treating rheumatoid arthritis.

15. Use as claimed in Claim 14 wherein the enzyme is a 3-phytase, 6-phytase, acid phosphatase, or a mixture thereof.

16. Use as claimed in Claim 14 or Claim 15 wherein the enzyme is 3-phytase EC 3.1.38.

17. Use as claimed in any one of claims 1 to 6, or 14 to 16 wherein the phytic acid, phytate salt, or an isomer or hydrolysate thereof is absorbed into a pharmaceutically acceptable carrier.

Claims for the following Contracting States: ES and GR

1. Use of phytic acid, a phytate salt, an isomer or hydrolysate of phytic acid or a phytate salt, or a mixture thereof for the manufacture of a medicament for treating rheumatoid arthritis.

2. Use as claimed in Claim 1 wherein the phytate salt comprises a potassium salt.

3. Use as claimed in Claim 2 wherein the phytate salt is mono- or di-potassium phytate, or a mixture thereof.

4. Use as claimed in Claim 1 wherein the isomers of phytic acid or phytate salt comprise the hexakisphosphate myo-inositol, scyllo-inositol, D-chiro-inositol, L-chiro inositol, neo-inositol and muco-inositol conformations.

5. Use as claimed in Claim 4 wherein the isomer of phytic acid or phytate salt is the hexakisphosphate myo-inositol conformation.

6. Use as claimed in Claim 1 wherein the hydrolysate of phytic acid or phytate salt comprises the pentakisphosphate, tetrakisphosphate, triphosphate, diphosphate, monophosphate or completely dephosphorylated hydrolysate.

7. A process for the preparation of a pharmaceutical composition for use in the treatment of rheumatoid arthritis which comprises mixing a pharmaceutically effective amount of phytic acid, a phytate salt, an isomer or hydrolysate of phytic acid or a phytate salt, or a mixture thereof in combination with a dephosphorylating enzyme with a pharmaceutically acceptable diluent or carrier.

8. A process as claimed in Claim 7 wherein the enzyme is 3-phytase, 6-phytase, acid phosphatase, or a mixture thereof.

9. A process as claimed in Claim 7 or Claim 8 wherein the enzyme is 3-phytase EC 3.1.38.

10. A composition which comprises phytic acid, a phytate salt, an isomer or hydrolysate of phytic acid or a phytate salt or a mixture thereof in combination with a dephosphorylating enzyme, for the use as a medicament for treating rheumatoid arthritis.

11. A Composition as claimed in Claim 10 wherein the enzyme is 3-phytase, 6-phytase, acid phosphatase, or a mixture thereof.

12. A composition as claimed in Claim 10 or Claim 11 wherein the enzyme is 3-phytase EC 3.1.38.

13. A composition as claimed in Claim 10 to 12 which is in the form of a pharmaceutical composition

tion prepared by a process as claimed in Claim 7.

14. Use of phytic acid, a phytate salt, an isomer or hydrolysate of phytic acid or a phytate salt, or a mixture thereof, in combination with a dephosphorylating enzyme for the manufacture of a medicament for treating rheumatoid arthritis. 5

15. Use as claimed in Claim 14 wherein the enzyme is a 3-phytase, 6-phytase, acid phosphatase, or a mixture thereof.

16. Use as claimed in Claim 14 or Claim 15 wherein said enzyme is 3-phytase EC 3.1.38. 10

17. Use as claimed in any one of claims 1 to 6 and 14 to 16 wherein the phytic acid, phytate salt or an isomer, or hydrolysate thereof is absorbed into a pharmaceutically acceptable carrier. 15

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